

References

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 NOTE: (Medline: 94235369) CTL restricted by several different class I molecule HLA types can present this V3 antigen: RIQRGPGRAFVTIGK, HLA A11.
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 NOTE: (Medline: 93342850) Both HLA A2 and A3 class I molecules types can present this V3 antigen: RIQRGPGRAFVTIGK .
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HIV CTL Epitopes

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NOTE: (Medline: 96159130) The same set of four peptides from the Rev protein could stimulate proliferation of CD4+ cells and trigger CTL killing of autologous target cells transformed with EBV.

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NOTE: (Medline: 97170967) Genetic pathways of virus escape from CTL pressure resembled virus escape from antiretroviral therapy.

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[Brander et al.(1995a)] C. Brander, W. J. Pichler, & G. Corradin. Identification of HIV protein derived cytotoxic T-lymphocyte (CTL) epitopes for their possible use as synthetic vaccines. *Clin Exp Immunol* **101**:107–113, 1995a.

NOTE: (Medline: 95325623) To identify CTL epitopes with potential as peptide-vaccine candidates, peptide sequences were screened for fulfilling the HLA-A2.1 binding motif and involvement in the natural immune response to HIV. Five peptides bound to HLA-A2.1, and HIV-infected persons showed a cytotoxic response against peptide-labeled target cells.

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NOTE: (Medline: 93124561) Using autologous Epstein-Barr virus transformed cells that were infected with vaccinia constructs carrying p18, p24 and p55 proteins of LAI, or truncations of p24, it was shown that epitopes within p24 were most commonly recognized in a set of cell lines derived from 29 infected subjects. The autologous transformed cells coated with synthetic peptides were used to identify several regions of p24 where CTL epitopes tended to cluster. HLA restriction was determined CTL responsive to four of the peptides. Among the four epitopes that had determined HLA specificities were the two peptides in the study that proved to stimulate CTL from the highest fraction of the cell lines: peptide p24(263-272) HLA-B27 and peptide p24(256-270) HLA-A33; these peptides were each able to stimulate CTL response from 14% of the cell lines.

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NOTE: (Medline: 92357052) Peptide competition experiments for presentation of viral peptides restricted by HLA-A3 and HLA-B27 was performed to study the specificity of peptide binding to class I molecules. HIV-1 Nef (74-82) presentation by HLA-A3 was among the epitopes studied.

HIV CTL Epitopes

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NOTE: (Medline: 95373144) Seven diverse V3 peptides were found to induce CTL in immunized mice. All contained the H-2D^d binding motif G, P and R at positions 2, 3 and 5. Only a CTL, and no antibody response, was detected in immunized mice.

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NOTE: (Medline: 90354794) 64 viral antigenic peptides HLA-A,B,C heavy chains, and clathrin light chains were tested for binding to HLA-A2.1, Aw68.1, Aw69, B44, and B5. 15 of the peptides including T cell epitopes, gave significant binding.

[Cheynier et al.(1992)] R. Cheynier, P. Langlade-Demoyen, M. R. Marescot, S. B. S., G. Blondin, S. Wain-Hobson, C. Griscelli, E. Vilmer, & F. Plata. Cytotoxic T lymphocyte responses in the peripheral blood of children born to human immunodeficiency virus-1-infected mothers. *Eur J Immunol* **22**:2211–2217, 1992.

NOTE: (Medline: 92387221) CTL effectors that killed HLA-matched HIV-1-infected H9 target cells or doubly transfected P815-A2-env, gag or nef mouse tumor cells, which expressed the viral antigens in association with HLA-A1/A3 or HLA-A2, were isolated in children born to HIV-1-infected mothers. HIV-1-specific CTL were detected less than 2 months after birth, and declined with disease progression. CTL were detected in the PBMC of three children who subsequently became seronegative.

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NOTE: (Medline: 89052758) Based on what was known about epitope structure and amino acid frequencies in 1988, the authors predicted epitopes in the *gag* proteins. Four peptides that were predicted to contain epitopes were found to specifically stimulate an HLA-A2 restricted polyclonal CTL cell line, when presented by mouse P815 target cells that had been transfected with HLA-A2.

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NOTE: (Medline: 91170774) Four peptides that could be used to stimulate helper T-cell function were also found to be reactive with MHC class I restricted CTL in infected individuals. 14 of 20 patients were responsive to at least one of the four peptides.

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NOTE: (Medline: 94170859) Peptides from influenza and HIV-1 tested for their ability to promote the assembly of HLA-A2 and HLA-B51 molecules in T2 cell lysates. HIV Pol 476-484 allowed significant assembly of HLA-A2, and is a target for CTL. Nef peptide 186-194 produced significant assembly of HLA-B51. A hydrophobic anchor residue (V, L, I) at position 9 could occupy pocket F, and a hydrophobic residue (V, L) at position 3 or 4 may anchor to hydrophobic pocket D of HLA-B51. Proline at position 2 increases HLA-B51 anchoring.

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NOTE: (Medline: 95220421) Viral sequences across this region were compared from 3 HLA-A11 positive and 10 negative donors. Substitutions that were found only in the 3 HLA-A11 donors did not promote HLA-A11 assembly. Substitution that were found in both HLA-A11 positive and negative donors, however, did not markedly alter the reactivity of the peptides. This suggests that substitutions that result in loss of HLA-A11 occur mainly in HLA-A11 positive donors.

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NOTE: (Medline: 95220421) HIV-1 HLA-A11 and -B18 restricted epitopes were sequenced from donors who do and do not express the HLA-A11 and B18 molecule. Selective variations were only detected in virus isolated from individuals expressing the appropriate HLA type. Variant peptides with single substitutions within the minimal epitope did not always completely abrogate HLA binding, suggesting that multiple alterations within a particular epitope may need to accumulate during disease progression to allow viral escape.

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NOTE: (Medline: 91132023) Nef specific CTL were generated from six seropositive donors. Six epitopes were defined, all localized to two regions in the central part of Nef. Some epitopes could be recognized in the contexts of several HLA class I molecules. Peptides were based on BRU epitopes: QVPLRPMTYK, HLA A3, A11, B35; AAVDLSHFLKEK, HLA A11; HTQGYFPQWQ, HLA B17; TQGYFPQWQNYT, HLA B17, B37; NYTPGPGVRYPLT, HLA B7; and GVRYPPLTFGWCYKLVP, HLA B18).

[Culmann et al.(1989)] B. Culmann, E. Gomard, M. P. Kieny, B. Guy, F. Dreyfus, & A. G. Saimot. An antigenic peptide of the HIV-1 NEF protein recognized by cytotoxic T lymphocytes of seropositive individuals in association with different HLA-B molecules. *Eur J Immunol* **19**:2383–2386, 1989.

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NOTE: (Medline: 92013025) Using synthetic peptides, six conserved epitopes on gp120 Env were identified, recognized by polyclonal human CTL in association with HLA-A2 class I. Conserved epitopes: RIQRGP-GRAFVTIGK, IIIB; LWVTVYYGVPVKEATTLFCA; TTSYTLTSCNTSVITQACPK; SVEINC-TRPNNNTRKSI; PEIVTHS; KNCGGEFFYCNS; LPCRIKQFINMWQEVGKAMY; VKIEPLGVAP-TKAKRRVVQR. control: gag, YKRWIILGLNKIVRMYSP, HLA B27.

[Dai et al.(1992)] L. C. Dai, K. West, R. Littaua, K. Takahashi, & F. A. Ennis. Mutation of human immunodeficiency virus type 1 at amino acid 585 on gp41 results in loss of killing by CD8+ A24-restricted cytotoxic T lymphocytes. *J Virol* **66**:3151–3154, 1992.

NOTE: (Medline: 92219406) An A24-restricted CD8+ CTL gp41 epitope was localized: YLKDDQQLL, using a CTL clone from an HIV infected individual. Lys to (Arg or Gln) substitution in peptides used to pulse a target cell line eliminated killing.

HIV CTL Epitopes

[De Groot et al.(1991)] A. S. De Groot, M. Clerici, A. Hosmalin, S. H. Hughes, D. Barnd, C. W. Hendrix, R. Houghten, G. M. Shearer, & J. A. Berzofsky. Human immunodeficiency virus reverse transcriptase T-helper epitopes identified in mice and humans: correlation with a cytotoxic T-cell epitope. *J Infect Dis* **164**:1058–1065, 1991.

NOTE: (Medline: 92064980) This peptide stimulates both murine helper and cytotoxic T-cells and was able to stimulate IL-2 producing T-cells from 9 out of 17 HIV seropositive humans. RT epitope: CTE-MEKEGKISKIGP.

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[DiBrino et al.(1994a)] M. DiBrino, K. C. Parker, D. H. Margulies, J. Shiloach, R. V. Turner, M. Garfield, W. E. B. WE, & J. E. Coligan. The HLA-B14 peptide binding site can accommodate peptides with different combinations of anchor residues. *J Biol Chem* **269**, 1994a.

NOTE: (Medline: 95096094).

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NOTE: (Medline: 94110616).

[Doe & Walker(1997)] B. Doe & C. M. Walker. HIV-1 p24 Gag-specific cytotoxic T-lymphocyte responses in mice. *AIDS* **10**:793–794, 1997.

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NOTE: (Medline: 96185988) Mice immunized with this peptide had an active CTL response that could be specifically tolerized with continued administration of soluble peptide; this was also observed with a malaria peptide. Suggests that soluble peptide may be useful for treatment of autoimmune disease.

[Dupuis et al.(1995)] M. Dupuis, S. K. Kundu, & T. C. Merigan. Characterization of HLA-A*0201-restricted cytotoxic T-cell epitopes in conserved regions of the HIV type 1 gp160 protein. *J Immunol* **155**:2232–2239, 1995.

NOTE: (Medline: 95363191) Five HLA-A2 HIV-1 seropositive HIV-1 MN rec gp160 vaccinees had their CTL activity assessed using peptides known to bind with high affinity to HLA-A*0201. Four of the patients had specific CTL activity for a minimum of at least three epitopes, thus the response appears heterogeneous. One of the four peptides was confirmed to be HLA A2 restricted. Epitopes were highly conserved.

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Y. Igarashi, Y. Ichikawa, & R. F. Siliciano. Class I-restricted presentation of an HIV-1 gp41 epitope

containing an N-linked glycosylation site. *J. Immunol.* **156**:834–840, 1996.

NOTE: (Medline: 96133015) The class I processing pathway usually begins in the cytosol. Env proteins are co-translationally located in the endoplasmic reticulum, where they are glycosylated, and in general are not found in the cytosol. The N-linked glycosylation site was not occupied in the TAVPWNASW naturally processed peptide presented by B*3501, and the non-glycosylated form was the form recognized by a env-specific CTL clone. This suggests that there may be limited failure of translocation, resulting in synthesis and degradation in the cytosol, and entry in the normal class I processing pathway.

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NOTE: (Medline: 97057743) This paper is correspondence breifly describing the identification and characterization of an immuno-dominat A26-CTL epitope in an asymptomatic HIV+ individual.

[Goulder et al.(1997a)] P. Goulder, A. Sewell, D. Laloo, D. Price, J. Whelan, J. Evans, G. Taylor, G. Luzzi, P. Giangrande, R. Phillips, & A. J. McMichael. Patterns of immunodominance in hiv-1-specific cytotoxic T lymphocyte responses in two human histocompatibility leukocyte antigens (HLA)-identical siblings with hla-a*0201 are influenced by epitope mutation. *J Exp Med* **8**:1423–33, 1997a.

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HIV CTL Epitopes

[Goulder et al.(1997b)] P. J. Goulder, A. Edwards, R. E. Phillips, & A. J. McMichael. Identification of a novel HLA-B*3501-restricted cytotoxic T lymphocyte epitope using overlapping peptides. *AIDS* **11**(7):930–932, 1997b.

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[Goulder et al.(1997c)] P. J. Goulder, A. Edwards, R. E. Phillips, & A. J. McMichael. Identification of a novel HLA-B*2705-restricted cytotoxic T lymphocyte epitope within a conserved region of HIV-1 Nef. *AIDS* **11**:536–538, 1997c.

NOTE: (Medline: 97239113).

[Goulder et al.(1996b)] P. J. R. Goulder, M. Bunce, P. Krausa, K. McIntyre, S. Crowley, B. Morgan, A. Edwards, P. Giangrande, R. E. Phillips, & A. J. McMichael. Novel, cross-restricted, conserved and immunodominant cytotoxic T lymphocyte epitopes in slow HIV type 1 infection. *AIDS Res and Hum Retroviruses* **12**:1691–1698, 1996b.

NOTE: (Medline: 97118362) HLA-B*57 is over-represented in slow progressors. HLA*5801 is a closely related molecule, and while the defined anchor residues of HLA*5801 can be used to predict epitopes in HIV-1 proteins, the CTL from HLA-B*57 positive individuals have limited cross-presentation capacity with HLA*5801 targets. In this paper five new HLA-B*57 epitopes were defined.

[Goulder et al.(1997d)] P. J. R. Goulder, R. E. Phillips, R. A. Colbert, S. McAdam, G. Ogg, M. A. Nowak, P. Giangrande, G. Luzzi, B. Morgan, A. Edwards, A. McMichael, & S. Rowland-Jones. Late escape from an immunodominant cytotoxic T-lymphocyte response associated with progression to AIDS. *Nature Med* **3**:212–216, 1997d.

NOTE: (Medline: 97170968) The CTL response was studied in six HIV+ individuals who make a strong immunodominant response to the same B27 epitope. In two donors and escape mutation arose after close to 10 years of epitope stability, around the time of progression to AIDS.

[Goulder et al.(1997e)] P. J. R. Goulder, S. W. Reid, D. A. Price, C. A. O'Callaghan, A. J. McMichael, R. E. Phillips, & E. Y. Jones. Combined structural and immunological refinement of HIV-1 HLA-B8 restricted cytotoxic T lymphocyte epitopes. *Eur J Immunol* **27**:1515–1521, 1997e.

NOTE: (Medline: 97353247).

[Griffiths et al.(1993)] J. Griffiths, S. J. Harris, G. T. Layton, E. L. Berrie, T. J. French, N. R. Burns, S. E. Adams, & A. J. Kingsman. Hybrid human immunodeficiency virus gag particles as an antigen carrier system: induction of cytotoxic T-cell and humoral responses by a gag:V3 fusion. *J Virol* **67**:3191–3198, 1993.

NOTE: (Medline: 91087316).

[Haas et al.(1996)] G. Haas, U. Plikat, P. Debre, M. Lucchiari, C. Katlama, Y. Dudoit, O. Bonduelle, M. Bauer, H. Ihlenfeldt, G. Jung, B. Maier, A. Meyerhans, & B. Autran. Dynamics of viral variants in HIV-1 Nef and specific cytotoxic T lymphocytes in vivo. *J Immunol* **157**:4212–4221, 1996.

NOTE: (Medline: 97047818).

[Hadida et al.(1995)] F. Hadida, G. Haas, G. Zimmermann, A. Hosmalin, R. Spohn, A. Samri, G. Jung, P. Debre, & B. Autran. CTL's from lymphoid organs recognize an optimal HLA-A2 restricted and HLA-B52 restricted nonapeptide and several epitopes in the C-terminal region of HIV-1 Nef. *J Immunol* **154**:4174–4186, 1995.

NOTE: (Medline: 95221926) An *in vitro* limiting dilution analysis showed CTL recognition in the context of HLA B52 and A2.1, A2.2 and A2.4 in nanomolar concentrations. Molecular modeling suggests motifs important for peptide binding to the pocket of an HLA-A2.1 molecule.

[Hadida et al.(1992)] F. Hadida, A. Parrot, M. P. Kieny, B. Sadat-Sowti, C. Mayaud, & P. Debre. Carboxyl-terminal and central regions of human immunodeficiency virus-1 NEF recognized by cytotoxic T lymphocytes from lymphoid organs. an *in vitro* limiting dilution analysis. *J Clin Invest* **89**:53–60, 1992.

NOTE: (Medline: 95221926) HIV-1 specific CTL can be detected in lymph nodes and spleens. The carboxyl-terminal domain of NEF is recognized by CTL in association with HLA-A1 and B8, with clonal frequencies of one CTL per 10^{-5} to 10^{-6} splenic lymphocytes.

[Hamajima et al.(1997)] K. Hamajima, J. Fukushima, H. Bukawa, T. Kaneko, T. Tsuji, Y. Asakura, S. Sasaki, K. Q. Xin, & K. Okuda. Strong augment effect of IL-12 expression plasmid on the induction of HIV-specific cytotoxic T lymphocyte activity by a peptide vaccine candidate. *Clin Immunol Immunopathol* **83**:179–84, 1997.

NOTE: (Medline: 97288401).

[Hammond et al.(1995)] S. A. Hammond, R. P. Johnson, S. A. Kalams, B. D. Walker, M. Takiguchi, J. T. Safrit, R. A. Koup, & R. F. Siliciano. An epitope-selective, transporter associated with antigen presentation TAP-1/2-independent pathway and a more general TAP-1/2-dependent antigen-processing pathway allow recognition of the HIV-1 envelope glycoprotein by CD8+ CTL. *J Immunol* **154**:6140–6156, 1995.

NOTE: (Medline: 95271010) Two peptide processing pathways are utilized for MHC class I presentation of HIV-1 Env epitopes. The previously characterized TAP-1 and TAP-2 dependent pathway can generate all Env epitopes and uses Env protein mislocalized in the cytosol to produce peptides. The second, novel pathway uses a TAP-1/2 independent pathway, and allows a subset of MHC restricted epitopes to be processed in the endoplasmic reticulum or a Golgi compartment.

[Hammond et al.(1991)] S. A. Hammond, E. Obah, P. Stanhope, C. R. Monell, M. Strand, F. M. Robbins, W. B. Bias, R. W. Karr, S. Koenig, & R. F. Siliciano. Characterization of a conserved T-cell epitope in HIV-1 gp41 recognized by vaccine-induced human cytolytic T-cells. *J Immunol* **146**:1470–1477, 1991.

NOTE: (Medline: 91132009) A HLA DPw4.2 human CTL epitope located in gp41 was described, recognized by CD4+ CTL clones that were induced in seronegative humans by immunization with recombinant gp160 BRU. gp41 CTL epitope: GIKQLQARILAVERYLKDQ.

[Harrer et al.(1996a)] E. Harrer, T. Harrer, P. Barbosa, M. Feinberg, R. P. Johnson, S. Buchbinder, & B. D. Walker. Recognition of the highly conserved YMDD region in the human immunodeficiency virus type 1 reverse transcriptase by HLA-A2-restricted cytotoxic T lymphocytes from an asymptomatic long-term nonprogresser. *J Inf Dis* **173**:476–479, 1996a.

NOTE: (Medline: 96162113) The amino acid stretch YMDD is a critical functional domain of reverse transcriptase, and is highly conserved. This sequence is also part of an HLA-A2-restricted epitope. The substitution YMDD to YVDD confers drug resistance to FTC and dideoxyinosine, and also abolishes the CTL specific response.

[Harrer et al.(1996b)] T. Harrer, E. Harrer, S. A. Kalams, P. Barbosa, A. Trocha, R. P. Johnson, T. Elbeik, M. B. Feinberg, S. P. Buchbinder, & B. D. Walker. Cytotoxic T lymphocytes in asymptomatic long-term nonprogressing HIV-1 infection. breadth and specificity of the response and relation to in vivo viral quasispecies in a person with prolonged infection and low viral load. *J Immunol* **156**:2616–2623, 1996b.

NOTE: (Medline: 96180222).

[Hickling et al.(1990)] J. K. Hickling, C. M. Fenton, K. Howland, S. G. Marsh, & J. B. Rothbard. Peptides recognized by class I restricted T-cells also bind to MHC class II molecules. *International Immunology* **2**:435–441, 1990.

NOTE: (Medline: 91197875) Peptides shown to be presented in the context of MHC class I proteins by mouse or human CD8+ T lymphocytes could also bind to HLA-DR molecules on the surface of B lymphoblastoid cell lines (B-LCL). Four out of five class I restricted T cell determinants bound, including the HIV-1 gp120 epitope.

HIV CTL Epitopes

[Hill et al.(1992)] A. V. Hill, J. Elvin, & A. C. W. et al. Characteristics of peptides eluted from HLA-B7. *Nature* **360**:434–439, 1992.

NOTE: (Medline: 93078872).

[Hosmalin et al.(1990)] A. Hosmalin, M. Clerici, R. Houghten, C. D. Pendleton, C. Flexner, D. R. Lucey, B. Moss, R. N. Germain, G. M. Shearer, & J. A. Berzofsky. An epitope in human immunodeficiency virus 1 reverse transcriptase recognized by both mouse and human cytotoxic T lymphocytes. *Proc Natl Acad Sci USA* **87**:2344–2348, 1990.

NOTE: (Medline: 90192804).

[Jardetzky et al.(1991)] T. S. Jardetzky, W. S. Lane, R. A. Robinson, D. R. Madden, & D. C. Wiley. Identification of self peptides bound to purified HLA-B27. *Nature* **353**:326–9, 1991.

NOTE: (Medline: 92018188).

[Jassoy et al.(1993)] C. Jassoy, T. Harrer, T. Rosenthal, B. A. Navia, J. Worth, R. P. Johnson, & B. D. Walker. Human immunodeficiency virus type 1-specific cytotoxic T lymphocytes release gamma interferon, tumor necrosis factor alpha (TNF-alpha), and TNF-beta when they encounter their target antigens. *J Virol* **67**:2844–2852, 1993.

NOTE: (Medline: 93233253) In this study the ability of HIV-1-specific CTL clones derived from seropositive persons to release gamma interferon (IFN- γ), tumor necrosis factor alpha (TNF- α), and TNF- β upon contact with target cells presenting viral antigen was assessed. Epitopes: p17: KIRLRPGGKKKYKLKHIVWASRELE, A3; gp41: VERYLKDQQL, B14 and A28; ERYLKDQQL, B14; RT: AIFQSSMTK-ILEPFRKQNPDIVIYQ, A11; and Nef SQRRQDILDLWIYHTQGYFPDWQNY, B13.

[Jassoy et al.(1992)] C. Jassoy, R. P. Johnson, B. A. Navia, J. Worth, & B. D. Walker. Detection of a vigorous HIV-1 specific cytotoxic T lymphocyte response in cerebrospinal fluid from infected persons with AIDS dementia complex. *J Immunol* **149**:3113–3119, 1992.

NOTE: (Medline: 93017933) CTL clones derived from CSF of individuals with AIDS dementia. HIV-1 specific CTL were detected in CSF from 5 out of 6 patients who were suffering from HIV-1 associated cognitive/motor complex disturbances.

[Johnson et al.(1994a)] R. P. Johnson, S. A. Hammond, A. Trocha, R. F. Siliciano, & B. D. Walker. Epitope specificity of MHC restricted cytotoxic T lymphocytes induced by candidate HIV-1 vaccine. *AIDS Research and Hum Retroviruses* **10**, Supp 2:S73–S75, 1994a.

NOTE: (Medline: 95169519) Volunteers were immunized with recombinant vaccinia virus expressing HIV-1 gp160 (vac-env) and boosted with recombinant gp160 (rgp160). CTL clones were analyzed for HLA restriction and specificity. An immunodominant HLA-A3.1 restricted epitope was observed that showed very little sequence variation among B subtype sequences, (TVYYGVPVWK). Naturally occurring variants of this peptide were able to stimulate reactivity. Two additional CD8+ CTL epitopes from vaccinees were characterized, as well as two CD4+ CTL epitopes.

[Johnson et al.(1994b)] R. P. Johnson, S. A. Hammond, A. Trocha, R. F. Siliciano, & B. D. Walker. Induction of a major histocompatibility complex class I-restricted cytotoxic T-lymphocyte response to a highly conserved region of human immunodeficiency virus type 1 (HIV-1) gp120 in seronegative humans immunized with a candidate HIV-1 vaccine. *J Virol* **68**:3145–3153, 1994b.

NOTE: (Medline: 94202302) In two volunteers, immunization with a single strain of HIV-1 induced CD4+ and CD8+ CTL that are specific for multiple conserved regions of HIV-1 and would be expected to recognize a broad range of viral isolates. The immunodominant gp120 epitope, gp120 TVYYGVPVWK, elicited CD8+ HLA-A3.1 restricted CTL, and this epitope is highly conserved. CTL specific for this epitope could lyse target cells sensitized with all known natural sequence variants. Additionally, CD8+ HLA-B35 and CD8+ HLA-B18 restricted epitopes were defined as well as two CD4+ cytotoxic T-cell gp120 epitopes: ITQACPKVSFEPIPHYCAPAGFAI and NNTLKQIDSKLREQFG.

[Johnson et al.(1992)] R. P. Johnson, A. Trocha, T. M. Buchanan, & B. D. Walker. Identification of overlapping HLA class I-restricted cytotoxic T-cell epitopes in a conserved region of the human immunodeficiency virus type 1 envelope glycoprotein: definition of minimum epitopes and analysis of the effects of sequence variation. *J Exp Med* **175**:961–971, 1992.

NOTE: (Medline: 92202878) Fine mapping and mutational analysis of gp41 epitopes: ERYLKDQQL, HLA B14 and YLKDQQLL, HLA B8.

[Johnson et al.(1993)] R. P. Johnson, A. Trocha, T. M. Buchanan, & B. D. Walker. Recognition of a highly conserved region of human immunodeficiency virus type 1 gp120 by an HLA-Cw4-restricted cytotoxic T-lymphocyte clone. *J Virol* **67**:438–445, 1993.

NOTE: (Medline: 93100827) The epitope sequence FNCGGEFF stimulates CTL response; the natural variants FNCRGEFF (SF2), TNCRGEFL (ROD) and LNCGGEFF (NDK) do not serve as epitopes. This was the first report of an HIV antigen specific target cells restricted by an HLA-C molecule, Cw4.

[Johnson et al.(1991)] R. P. Johnson, A. Trocha, L. Yang, G. P. Mazzara, D. L. Panicali, T. M. Buchanan, & B. D. Walker. HIV-1 gag-specific cytotoxic T lymphocytes recognize multiple highly conserved epitopes. fine specificity of the gag-specific response defined by using unstimulated peripheral blood mononuclear cells and cloned effector cells. *J Immunol* **147**:1512–1521, 1991.

NOTE: (Medline: 91349569) This study presented a detailed study of gag specific CTL from HIV-1 seropositive individuals. Seven p24 and two p17 epitopes were described, that were recognized by class I restricted CD3+CD8+ CTL. p17 epitopes: KIRLRPGGKKKYKLKHIVWASRELE and QTGSEELRSLYNTVATLYCVHQRIE; p24 epitopes: NPPIPVGEIYKRWIILGLNKIV, VHQAISPRTLNAAVVKVVEEKAF, NAWVKVVEEKAFSPEVIPMFSA, SALSEGATPQDL-NTMLNTVGHH, GHQAAMQMLKETINEAAEWDR, and RAEQASQEVK.

[Johnson & Walker(1994)] R. P. Johnson & B. D. Walker. CTL in HIV-1 infection: Responses to structural proteins. *Curr Topics Microbiol Immunol* **189**:35–63, 1994.

NOTE: (Medline: 95008926) Review.

[Kalams et al.(1994)] S. Kalams, R. P. Johnson, A. K. Trocha, M. J. Dynan, H. S. Ngo, R. T. D'Aquila, J. T. Kurnick, & B. D. Walker. Longitudinal analysis of T-cell receptor (TCR) gene usage by HIV-1 envelope-specific cytotoxic T-lymphocyte clones reveals a limited TCR repertoire. *J. Exp. Med.* **179**:1261–1271, 1994.

NOTE: (Medline: 94194282) This paper presents an in depth longitudinal study of T-cell receptor gene usage to a well defined HLA B14 restricted gp41 epitope. Ten CTL clones were derived from a single individual over 31 months. T-cell receptor V-D-J sequencing was performed on PCR amplification products. All ten clones utilized $V\alpha 14$ and $V\beta 4$ genes; observed limited T-cell receptor diversity to an immunodominant epitope was suggested to facilitate immune escape. gp41 epitope: ERYLKDQQL. An HLA B14 restricted RT epitope from this individual used $V\alpha 21$ and $V\beta 14$, showing use of these genes was not a feature of all HLA B14 restricted clones from this individual. RT epitope: AIYLALQDSGLEVNIVTDSQYALGI.

[Kalams et al.(1996)] S. A. Kalams, R. P. Johnson, M. J. Dynan, K. E. Hartman, T. Harrer, E. Harrer, A. K. Trocha, W. A. Blattner, S. P. Buchbinder, & B. D. Walker. T cell receptor usage and fine specificity of human immunodeficiency virus type 1 specific cytotoxic T lymphocyte clones: analysis of quasispecies recognition reveals a dominant response directed against a minor in vivo variant. *J Exp Med* **183**:1699–1679, 1996.

NOTE: (Medline: 96261668).

[Kast et al.(1994)] W. M. Kast, R. M. Brandt, J. Sidney, J. W. Drijfhout, R. T. Kubo, H. M. Grey, C. J. Melief, & A. Sette. Role of HLA-A motifs in identification of potential CTL epitopes in human papillomavirus type 16 E6 and E7 proteins. *J Immunol* **152**:3904–3912, 1994.

NOTE: (Medline: 94194153) Binding affinities for five HLA-A alleles: HLA-A1 (A*0101), A2.1 (A*0201), A3 (A*0301), A11 (A*1101), and A24 (A*2401) was determined for all nonamer peptides of human papillomavirus type 16 E6 and E7. High affinity binding peptides allowed an assessment of binding-motifs.

HIV CTL Epitopes

[Kent et al.(1997)] S. J. Kent, P. D. Greenberg, M. C. Hoffman, R. E. Akridge, & M. J. McElrath. Antagonism of vaccine-induced HIV-1-specific CD4+ T cells by primary HIV-1 infection: potential mechanism of vaccine failure. *J Immunol* **158**:807–15, 1997.

NOTE: (Medline: 97146051) A vaccinia-gp160 vaccinee made a strong CD4+ T cell responses, including proliferative and cytolytic responses, but was infected anyway. The infecting virus had an escape mutant that could also serve as an antagonist.

[Kim et al.(1997)] D. T. Kim, D. J. Mitchell, D. G. Brockstedt, L. Fong, G. P. Nolan, C. G. Fathman, E. G. Engleman, & J. B. Rothbard. Introduction of soluble proteins into the MHC class I pathway by conjugation to an HIV tat peptide. *J Immunol* **159** (4):1666–1668, 1997.

NOTE: (Medline: 97400332) A vaccine based on the conjugation of OVA to a HIV Tat peptide that enhances protein uptake by APC cells stimulated MHC Class I-restricted T cell response *in vitro* and CTL generation *in vivo* in a murine system.

[Klenerman et al.(1996)] P. Klenerman, G. Luzzi, K. McIntyre, R. Phillips, & A. McMichael. Identification of a novel HLA-A25 restricted epitope in a conserved region of p24 gag (positions 71-80). *AIDS* **10**:348–350, 1996.

NOTE: (Medline: 97037037).

[Klenerman et al.(1995)] P. Klenerman, U.-C. Meier, R. E. Phillips, & A. J. McMichael. The effects of natural altered peptide ligands on the whole blood cytotoxic T lymphocyte response to human immunodeficiency virus. *Eur. J. Immunol.* **25**:1927–1931, 1995.

NOTE: (Medline: 95347391), This paper explores naturally occurring altered peptide ligands and their ability to sustain CTL, serve as antagonist to CTL specific for other variants, and to allow cell killing. The authors propose that a CTL response may be sustained *in vivo* that fails to recognize viral variants as they arise, proposing a mechanism for T-cell original antigenic sin.

[Klenerman et al.(1994)] P. Klenerman, S. Rowland-Jones, S. McAdam, J. Edwards, S. Daenke, D. Laloo, B. Koppe, W. Rosenberg, D. Boyd, A. Edwards, P. Giangrande, R. E. Phillips, & A. J. McMichael. Cytotoxic T-cell activity antagonized by naturally occurring HIV-1 Gag variants. *Nature* **369**:403–407, 1994.

NOTE:(Medline: 94255016) These paper documents that naturally occurring peptide variants can serve as antagonists, that is they can inhibit normal lysis of cells presenting the original epitope. The variants studied could serve as antagonists when they were processed from recombinant vaccinia, replicated HIV, or when they were synthetic peptides. Both agonist and antagonist sequences were found in the study subjects from whom the CTL clones were derived.

[Koenig et al.(1990)] S. Koenig, T. R. Fuerst, L. V. Wood, R. M. Woods, J. A. Suzich, G. M. Jones, V. F. de la Cruz, R. T. Davey Jr., S. Venkatesan, B. Moss, W. E. Biddison, & A. S. Fauci. Mapping the fine specificity of a cytotoxic T-cell response to HIV-1 Nef protein. *J Immunol* **145**:127–135, 1990.

NOTE: (Medline: 90293448) A 10 residue peptide that triggers CTL in association with the HLA A3.1 molecule was studied. Human cell transfectants were used to map a critical residue in the HLA A3.1 molecule for recognition, amino acid 152, which is present on the alpha-2 helix in HLA-A3.1 and is modified in the HLA A3.2 A3 allele.

[Konya et al.(1997)] J. Konya, G. Stuber, A. Bjorndal, E. M. Fenyo, & J. Dillner. Primary induction of human cytotoxic lymphocytes against a synthetic peptide of the human immunodeficiency virus type 1 protease. *J Gen Virol* **78**:2217–2224, 1997.

NOTE: (Medline: 97437476).

[Lapham et al.(1996)] C. Lapham, B. Golding, J. Inman, R. Blackburn, J. Manischewitz, P. Hightet, & H. Golding. *Brucella abortus* conjugated with a peptide derived from the V3 loop of human immunodeficiency virus (HIV) type 1 induces HIV-specific cytotoxic T-cell responses in normal and in CD4+ cell-depleted BALB/c mice. *J. Virol.* **70**:3084–3092, 1996.

NOTE: (Medline: 96186738).

[Layton et al.(1993)] G. T. Layton, S. J. Harris, A. J. Gearing, M. Hill-Perkins, J. S. Cole, J. C. Griffiths, N. R. Burns, A. J. Kingsman, & S. E. Adams. Induction of HIV-specific cytotoxic T lymphocytes in vivo with hybrid HIV-1 V3:Ty-virus-like particles. *J Immunol* **151**:1097–1107, 1993.

NOTE: (Medline: 95271010) V3-Ty-Virus-like particles can induce type specific CTL in mice in the absence of adjuvant.

[Leggatt et al.(1997)] G. R. Leggatt, M. A. Alexander-Miller, A. Kumar, S. L. Hoffman, & J. A. Berzofsky. Cytotoxic T lymphocyte (CTL) adherence assay (CAA): a non-radioactive assay for murine CTL recognition of peptide-MHC class I complexes. *J Immunol Methods* **201**:1–10, 1997.

NOTE: (Medline: 97184603) This paper describes a novel assay, the CTL adhesion assay (CAA), and uses an HIV epitope in a murine system as a model system. CAA is a rapid, simple screening method for identifying cytolytic epitopes for a given CTL line, and may also identify peptides that cause T cell activation and adherence but not cytolytic activity.

[Lieberman et al.(1997)] J. Lieberman, J. A. Fabry, D. M. Fong, & G. R. P. 3rd. Recognition of a small number of diverse epitopes dominates the cytotoxic T lymphocytes response to HIV type 1 in an infected individual. *AIDS Res Hum Retroviruses* **13**:383–92, 1997.

NOTE: (Medline: 97229916).

[Lieberman et al.(1992)] J. Lieberman, J. A. Fabry, M. Kuo, P. Earl, B. Moss, & P. R. Skolnik. Cytotoxic T lymphocytes from HIV-1 seropositive individuals recognize immunodominant epitopes in gp160 and reverse transcriptase. *J Immunol* **148**:2738–2747, 1992.

NOTE: (Medline: 92242898) This paper does not use T-cell clones to map epitopes, but rather T-cell lines from HIV infected donors. 20 amino acid peptides were used of map the region of the reactive epitopes. HLA restriction was not tested for all epitopes.

[Lieberman et al.(1995)] J. Lieberman, J. A. Fabry, P. Shankar, L. Beckett, & P. R. Skolnik. *Ex vivo* expansion of HIV type 1-specific cytolytic T cells from HIV type 1-seropositive subjects. *AIDS Res Hum Retroviruses* **11**:257–271, 1995.

NOTE: (Medline: 95260535) Potent HIV-specific CTL lines were developed through culture of non-specific stimulation of T cell lines with autologous antigen presenting cells preincubated with HIV-1 peptides.

[Littaua et al.(1991)] R. A. Littaua, M. B. A. Oldstone, A. Takeda, C. Debouck, J. T. Wong, C. U. Tuazon, B. Moss, F. Kievits, & F. A. Ennis. An HLA-C-Restricted CD8+ cytotoxic T-Lymphocyte clone recognizes a highly conserved epitope on human immunodeficiency virus type 1 gag. *J Virol* **65**:4051–4056, 1991.

NOTE: (Medline: 91303653) Fine mapping of gag p24 epitope with HLA-C restriction: QAISPR, HLA, Cw3.

[Lubaki et al.(1997)] N. M. Lubaki, S. C. Ray, B. Dhruva, T. C. Quinn, R. F. Siliciano, & R. C. Bollinger. Characterization of a polyclonal cytolytic T lymphocyte response to human immunodeficiency virus in persons without clinical progression. *J Infect Dis* **6**:1360–7, 1997.

NOTE: (Medline: 97323979) Five individuals were studied who survived HIV infection in good health for over 5 years. A broad polyclonal response was found to multiple proteins.

[Lubeck et al.(1997)] M. D. Lubeck, R. Natuk, M. Myagkikh, N. Kalyan, K. Aldrich, F. Sinangil, S. Alipanah, S. C. S. Murthy, P. K. Chanda, S. M. Nigida Jr., P. D. Markham, S. Zolla-Pazner, K. Steimer, M. Wade, M. S. Reitz Jr., L. O. Arthur, S. Mizutani, A. Davis, P. P. Hung, R. C. Gallo, J. Eichberg, & M. Robert-Guroff. Long-term protection of chimpanzees against high-dose HIV-1 challenge induced by immunization. *Nature Med* **3** No **6**:651–658, 1997.

NOTE: (Medline: 97319589).

[Macatonia et al.(1991)] S. E. Macatonia, S. Patterson, & S. C. Knight. Primary proliferative and cytotoxic T-cell responses to HIV induced in vitro by human dendritic cells. *Immunology* **74(3)**:399–406, 1991.

NOTE: (Medline: 92120708) A primary CTL response in cells from uninfected donors was detected by using a system where peptide was presented by human dendritic cells.

HIV CTL Epitopes

[McAdam et al.(1995)] S. McAdam, P. Klenerman, L. Tussey, S. Rowland-Jones, D. Laloo, R. Phillips, A. Edwards, P. Giangrande, A. L. Brown, & F. Gotch. Immunogenic HIV variant peptides that bind to HLA-B8 can fail to stimulate cytotoxic T lymphocyte responses. *J Immunol* **155**:2729–36, 1995.

NOTE: (Medline: 95378698).

[McMichael & Walker(1994)] A. J. McMichael & B. D. Walker. Cytotoxic T lymphocytes epitopes: implications for HIV vaccine. *AIDS* **8S**:S155–S173, 1994.

NOTE: (Medline: Comprehensive review summarizing CTL epitopes that have known HLA type and are fine mapped to indicate epitope boundaries. Anchor residues are indicated when known for different HLA restricted epitopes. Includes a summary of the published literature, as well as much work that was in press or submitted for publication.

[Meier et al.(1995)] U. Meier, P. Klenerman, P. Griffin, W. James, B. Koppe, B. Larder, R. E. Phillips, A. J. McMichael, & R. E. Phillips. Cytotoxic T lymphocyte lysis inhibited by viable HIV mutants. *Science* **270**:1360–1362, 1995.

NOTE: (Medline: 96085065) HIV bearing mutations in epitope allowed transactive inhibition of specific CTL mediated lysis. Therefore, mutations in epitopes may not only allow escape from specific CTL, but enhance the ability of wildtype virus to persist.

[Meyerhans et al.(1991)] A. Meyerhans, G. Dadaglio, J. P. Vartanian, P. Langlade-Demoyen, R. Frank, B. Asjo, F. Plata, & S. Wain-Hobson. *In vivo* persistence of a HIV-1-encoded HLA-B27-restricted cytotoxic T lymphocyte epitope despite specific *in vitro* reactivity. *Eur J Immunol* **21**:2637–2640, 1991.

NOTE: (Medline: 92008181) This study looked for the presence of CTL escape mutants *in vivo* in proviral DNA from an infected individual who had CTL activity; in 8 and 14 months escape mutants had not accumulated.

[Moss et al.(1995)] P. A. H. Moss, S. L. Rowland-Jones, P. M. Frodsham, S. McAdam, P. Giangrande, A. McMichael, & J. I. Bell. Persistent high frequency of human immunodeficiency virus-specific cytotoxic T cells in peripheral blood of infected donors. *Proc Nat Acad Sci USA* **92**:5773–5777, 1995.

NOTE: (Medline: 95320157).

[Musey et al.(1997)] L. Musey, Y. Hu, L. Eckert, M. Christensen, T. Karchmer, & M. J. McElrath. HIV-1 induces cytotoxic T lymphocytes in the cervix of infected women. *J Exp Med* **185**:293–303, 1997.

NOTE: (Medline: 97169071) Mononuclear cells in cytobrush specimens from the cervical samples were stimulated with antigen. Eight women with CD4 positive counts ≥ 500 cells/ μ l had HIV-1 specific CTL, but only 4/11 with counts < 500 cells/ μ l had HIV-1 specific CTL responses.

[Nakamura et al.(1997)] Y. Nakamura, M. Kameoka, M. Tobiume, M. Kaya, K. Ohki, T. Yamada, & K. Ikuta. A chain section containing epitopes for cytotoxic T, B and helper T cells within a highly conserved region found in the human immunodeficiency virus type 1 gag protein. *Vaccine* **5**:489–96, 1997.

NOTE: (Medline: 97304244).

[Nehete et al.(1995)] P. N. Nehete, K. S. Casement, R. B. Arlinghus, & K. J. Sastry. Studies on *in vivo* induction of HIV-1 Envelope-specific cytotoxic T lymphocytes by synthetic peptides from the V3 loop region of HIV-1 IIIB gp120. *Cellular Immunology* **160**:217–223, 1995.

NOTE: (Medline: 95236465).

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NOTE: (Medline: 95173425) Single point mutations were introduced into this epitope in the viral strain LAI, and the ability comparable peptides to sensitize target strains were tested. The change of anchor residue R 264 to (L or G), results in infectious virus, and corresponding peptide has reduced binding affinities for HLA-B27. The change of G 267 to K or E abrogated infectivity, and the peptide bound to HLA-B27, but did not serve as a target; thus nonrecognition of peptides derived from quasispecies analysis of a small region might not really be associated with an escape mutant, but rather a non-viable mutant.

[Nixon & McMichael(1988)] D. Nixon & A. J. McMichael. Cytotoxic T-cell recognition of HIV proteins and peptides. *AIDS* **5**:1049–1059, 1988.

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NOTE: (Medline: 89057146) p24 KRWIILGLNKIVRMY.

[Nixon et al.(1990)] D. F. Nixon, S. Huet, J. Rothbard, M. Kieny, M. Delchambre, C. Thiriart, C. R. Rizza, F. M. Gotch, & A. J. McMichael. An HIV-1 and HIV-2 cross-reactive cytotoxic T-cell epitope. *AIDS* **4**:841–845, 1990.

NOTE: (Medline: 91069449) A HLA-B27 specific CTL clone from an HIV-1 infected individual that reacts with the Gag SF2 epitope KRWIILGLNKIVRMY also cross-reacts with the HIV-2 ROD analog RRWIQIGLQLQKSVRMY. The CTL also reacts with HIV-1 ELI KRWIIVGLNKIVRMY and SIVmm142 RRWIQLGLQLQKSVRMY, but only at very high concentration of peptide with SIVk6w78 RRWIQLRLQKSVRMY. The binding of the SIVk6w78 peptide to HLA-B27 does not seem to be reduced, so the authors suggest that the reduced ability to stimulate is in this case due to T-cell receptor interaction.

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NOTE: (Medline: 92029720) p17: LRPGGKKKYKLKHIV, HLA B8 and p24: VQNANPDCKTILKAL, HLA B8.

[Nowak et al.(1995)] M. A. Nowak, R. M. May, R. E. Phillips, S. Rowland-Jones, D. G. Lalloo, S. McAdam, P. Klennerman, B. Koppe, K. Sigmund, C. R. M. Bangham, & A. J. McMichael. Antigenic oscillations and shifting immunodominance in HIV-1 infections. *Nature* **375**:606–611, 1995.

NOTE: (Medline: 95312083) This paper presents longitudinal studies of epitope variation and corresponding CTL responses in two patients. A mathematical model was created to provide a framework to explain the observed shifts in epitope and CTLp frequencies. For discussion, see also: J. M. Coffin, *Nature* **375**:534–535 (1995).

[Parker et al.(1994)] K. C. Parker, M. A. Bednarek, & J. E. Coligan. Scheme for ranking potential HLA-A2 binding peptides based on independent binding of individual peptide side-chains. *J Immunol* **152**, 1994.

NOTE: (Medline: 94075819) The authors conclude that peptide amino acid side-chain binding to the HLA-A2 molecule is independent of the sequence of the peptide, and developed a table of coefficients that can be used to help predict peptide binding to HLA-A2.

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NOTE: (Medline: 92086044) Fluctuations in the specificity of cytotoxic T-cells for HIV was correlated with variability in proviral gag (DNA) epitope sequences.

[Pinto et al.(1995)] L. A. Pinto, J. Sullivan, J. A. Berzofsky, M. Clerici, H. A. Kessler, A. L. Landay, & G. M. Shearer. Env-specific cytotoxic T lymphocyte responses in HIV seronegative health care workers occupationally exposed to HIV-contaminated body fluids. *J. Clin. Invest.* **96**:867–876, 1995.

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[Pogue et al.(1995)] R. R. Pogue, J. Eron, J. A. Frelinger, & M. Matsui. Amino-terminal alteration of the HLA-A*0201-restricted human immunodeficiency virus pol peptide increases complex stability and in vitro immunogenicity. *Proc Natl Acad Sci USA* **92**:8166–8170, 1995.

NOTE: (Medline: 95396758) In this mutational study a substitution of 476 I to Y did not increase affinity but did increase complex stability with HLA-A*0201. The altered peptide (Y) provided a greater stimulation of wildtype pol-specific CTL response relative to the wildtype peptide (I), in three different seropositive individuals.

[Porgador et al.(1997)] A. Porgador, H. F. Staats, B. Faiola, E. Gilboa, & T. J. Parker. Intranasal immunization with CTL epitope peptides from HIV-1 or ovalbumin and the mucosal adjuvant cholera toxin induces peptide- specific CTLs and protection against tumor development in vivo. *J Immunol* **158**:834–41, 1997.

NOTE: (Medline: 97146054).

[Price et al.(1997)] D. A. Price, P. J. Goulder, P. Klenerman, A. K. Sewell, P. J. Easterbrook, M. Troop, C. R. Bangham, & R. E. Phillips. Positive selection of HIV-1 cytotoxic T lymphocyte escape variants during primary infection. *Proc Natl Acad Sci USA* **94**:1890–5, 1997.

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NOTE: (Medline: 95087232) Cytokine release from stimulated CTL clones derived from either the peripheral blood or CSF of 3 patients was studied. HLA restriction was determined for two of seven clones. GM-CSF and TNF- α and IFN- γ were produced by all clones; most clones produced low amounts of IL-2, IL-3, and IL-4.

[Rammensee et al.(1995)] H.-G. Rammensee, T. Friede, & S. Stevanovic. Mhc ligands and peptide motifs: first listing. *Immunogenetics* **41**:178–228, 1995.

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[Robertson et al.(1993)] M. N. Robertson, F. Buseyne, O. Schwartz, & Y. Riviere. Efficient antigen presentation to cytotoxic T lymphocytes by cells transduced with a retroviral vector expressing the HIV-1 Nef protein. *AIDS Res and Hum Retroviruses* **9**:1217–1223, 1993.

NOTE: (Medline: 94190626) This paper presents a retroviral vector system for antigen presentation to CTLs. As part of the controls to test their system, they study the response to specific Nef peptides, which contain the dominant CTL epitopes in Nef in their study subject.

[Rowland-Jones et al.(1997)] S. Rowland-Jones, R. Tan, & A. McMichael. Role of cellular immunity in protection against HIV infection. In *Adv Immunol*, volume 65, pages 277–346. Academic Press, 1997.

NOTE: Review (Medline: 97381156) An comprehensive, excellent review of CTL immunity.

[Rowland-Jones et al.(1993a)] S. L. Rowland-Jones, D. F. Nixon, M. C. Aldhous, F. Gotch, K. Ariyoshi, N. Hallam, J. S. Kroll, K. Froebel, & A. McMichael. HIV-specific cytotoxic T-cell activity in an HIV-exposed but uninfected infant. *Lancet* **341**:860–861, 1993a.

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[Rowland-Jones et al.(1993b)] S. L. Rowland-Jones, S. H. Powis, J. Sutton, I. Mockridge, F. M. Gotch, N. Murray, A. B. Hill, W. M. Rosenberg, J. Trowsdale, & A. J. McMichael. An antigen processing polymorphism revealed by HLA-B8-restricted cytotoxic T lymphocytes which does not correlate with TAP gene polymorphism. *Eur J Immunol* **23**:1999–2004, 1993b.

NOTE: (Medline: 93345604) Individual fails to present HLA-B8-restricted influenza epitope, but can present an HLA-B8-restricted HIV-1 gag epitope.

[Rowland-Jones et al.(1995)] S. L. Rowland-Jones, J. Sutton, K. Ariyoshi, T. Dong, , F. Gotch, S. McAdam, D. Whitby, S. Sabally, A. Gallimore, T. Corrah, M. Takiguchi, T. Schultz, A. McMichael, & H. Whittle. HIV-specific cytotoxic T-cells in HIV-exposed but uninfected Gambian women. *Nature Medicine* **1**:59–64, 1995.

NOTE: (Medline: 96071373) Four HIV-1 and -2 cross-reactive epitopes that are presented to CTL from HIV-infected Gambians by HLA-35 were identified. These peptides could elicit HIV specific CTLs from 3 of 6 repeatedly exposed but seronegative sex workers who carry the HLA-B35 allele. Most CTL derived from HIV-2 positive donors also recognized the HIV-2 peptide and the analogous HIV-1 peptide.

[Safrit et al.(1994a)] J. T. Safrit, C. A. Andrews, T. Zhu, D. D. Ho, & R. A. Koup. Characterization of human immunodeficiency virus type 1-specific cytotoxic T lymphocyte clones isolated during acute seroconversion: recognition of autologous virus sequences within a conserved immunodominant epitope. *J Exp Med* **179**:463–472, 1994a.

NOTE: (Medline: 94125027) HIV-1 specific CTL clones were isolated from two individuals at acute seroconversion. In one patient, two HLA A31-restricted clones recognized the same fragment of gp41, peptide RLRDLLLIVTR, but one was sensitive to a Thr to Val substitution, while the other was not. A CTL HLA A32-restricted clone from the other patient recognized the gp41 peptide VLSIVNRVRQGYSPLSFQTH. Autologous viral sequences from seroconversion were recognized by the CTL clones, but not the HIV-1 strain MN.

[Safrit et al.(1994b)] J. T. Safrit, A. Y. Lee, C. A. Andrews, & R. A. Koup. A region of the third variable loop of HIV-1 gp120 is recognized by HLA-B7-Restricted CTLs from two acute seroconversion patients. *J Immunol* **153**:3822–3830, 1994b.

NOTE: (Medline: 95015873) HIV-1 envelope-specific CTL clones were isolated from the peripheral blood of two patients from within weeks of seroconversion. These clones were CD8+ and restricted by the HLA-B7 molecule. The minimum epitope was defined, RPNNNTRKSI, with anchor residues at the proline and isoleucine; the anchor residues are relatively well conserved. A serine to arginine change at position 9 of the epitope abrogated clone recognition in one of the patients. This amino acid change is one factor that has been associated with a change from a nonsyncytium-inducing to a syncytium-inducing phenotype of HIV-1.

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NOTE: (Medline: 97456556).

[Shankar et al.(1996)] P. Shankar, J. A. Fabry, D. M. Fong, & J. Lieberman. Three regions of HIV-1 gp160 contain clusters of immunodominant CTL epitopes. *Immunol Lett* **52**:23–30, 1996.

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[Shirai et al.(1997)] M. Shirai, S. Kozlowski, D. H. Margulies, & J. A. Berzofsky. Degenerate MHC restriction reveals the contribution of class I MHC molecules in determining the fine specificity of CTL recognition of an immunodominant determinant of HIV-1 gp160 V3 loop. *J Immunol* **158**:3181–8, 1997.

NOTE: (Medline: 97240759).

[Shirai et al.(1996)] M. Shirai, K. Kurokohchi, C. D. Pendleton, T. Arichi, L. F. Boyd, H. Takahashi, D. H. Margulies, & J. A. Berzofsky. Reciprocal cytotoxic T lymphocytes cross-reactivity interactions between two major epitopes within hiv-1 gp160. *J Immunol* **157**:4399–4411, 1996.

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[Shirai et al.(1992)] M. Shirai, C. D. Pendleton, & J. A. Berzofsky. Broad recognition of cytotoxic T cell epitopes from the HIV-1 envelope protein with multiple class I histocompatibility molecules. *J Immunol* **148**:1657–1667, 1992.

NOTE: (Medline: 92176620) This paper explored the possibility that defined epitopes from HIV-1 Env might be presented by multiple class I genes to CTLs using a murine system, isolating CTL from mice immunized with gp160 expressing recombinant vaccinia virus. The CTL epitope at the tip of the V3 loop (P18) was found to be presented by class I MHC molecules from four of ten haplotypes tested. Peptides that had previously been defined as helper T cell determinants (T1 in gp120, and HP53 (also called TH4.3)) were also able to stimulate CTL from mice with multiple haplotypes.

[Shirai et al.(1993)] M. Shirai, M. S. Vacchio, R. J. Hodes, & J. A. Berzofsky. Preferential V beta usage by cytotoxic T cells cross-reactive between two epitopes of HIV-1 gp160 and degenerate in class I MHC restriction. *J Immunol* **151**:2283–2295, 1993.

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[Siliciano et al.(1988)] R. Siliciano, T. Lawton, C. Knall, R. Karr, P. Berman, T. Gregory, & E. Reinherz. Analysis of host-virus interactions in AIDS with anti-gp120 T-cell clones: Effect of HIV sequence variation and a mechanism for CD4+ cell depletion. *Cell* **54**:561–575, 1988.

NOTE: (Medline: 88295131) This article demonstrated that a class II HLA-DR4 restricted response can be stimulated by CD4 uptake of gp120, suggesting a mechanism for T-cell depletion in vivo. This peptide containing the epitope was also able to stimulate a class I restricted, CD8+ CTL response.

[Sipsas et al.(1997)] N. V. Sipsas, S. A. Kalams, A. Trocha, S. He, W. A. Blattner, B. D. Walker, & R. P. Johnson. Identification of type-specific cytotoxic T lymphocyte responses to homologous viral proteins in laboratory workers accidentally infected with HIV-1. *J Clin Invest* **99**:752–62, 1997.

NOTE: (Medline: 97197584) To examine a situation where the autologous strain and the reference reagents would be the same, the CTL response of three lab workers accidentally infected with HIV IIIB was studied. Both group specific and type specific epitopes were targets for CTL clones. One subject had a broadening of CTL response over time, using a broad range of restricting HLA class I alleles.

[Smith et al.(1996)] K. J. Smith, S. W. Reid, D. I. Stuart, A. J. McMichael, E. Y. Jones, & J. I. Bell. An altered position of the alpha 2 helix of MHC class I is revealed by the crystal structure of HLA-B*3501. *Immunity* **4**:203–213, 1996.

NOTE: (Medline: 96209671) The crystal structure of HLA-B*3501 complexed with Nef epitope VPLRPMTY was determined at 2 angstrom resolution, revealing details about binding such as the structural basis for the tyrosine specificity of the F pocket.

[Steinle et al.(1996)] A. Steinle, K. Flak, O. Rotzschke, V. Gnau, S. Stevanovic, G. Jung, D. J. Schedel, & H. G. Rammensee. Motif of HLA-B*3503 peptide ligands. *Immunogenetics* **43**:105–107, 1996.

NOTE: (Medline: 96128264).

[Stuhler & Schlossman(1997)] G. Stuhler & S. F. Schlossman. Antigen organization regulates cluster formation and induction of cytotoxic T lymphocytes by helper T cell subsets. *Proc Natl Acad Sci USA* **94**:622–627, 1997.

NOTE: (Medline: 97165072) Generation of cytolytic activity requires a three-cell type cluster consisting of APC's, Helper, and CTL's, and co-expression of helper and CTL epitopes on the same APC. .

[Sutton et al.(1993)] J. Sutton, S. Rowland-Jones, W. Rosenberg, D. Nixon, F. Gotch, X. Gao, N. Murray, A. Spoonas, P. Driscoll, M. Smith, A. Willis, & A. McMichael. A sequence pattern for peptides presented to cytotoxic T lymphocytes by HLA B8 revealed by analysis of epitopes and eluted peptides. *Eur J Immunol* **23**:447–453, 1993.

NOTE: (Medline: 93170395).

[Takahashi et al.(1988)] H. Takahashi, J. Cohen, A. Hosmalin, K. B. Cease, R. Houghten, J. L. Cornette, C. DeLisi, B. Moss, R. N. Germain, & J. A. Berzofsky. An immunodominant epitope of the human immunodeficiency virus envelope glycoprotein gp160 recognized by class I major histocompatibility complex molecule-restricted murine cytotoxic T lymphocytes. *Proc Natl Acad Sci USA* **85**:3105–3109, 1988.

NOTE: (Medline: 88203649) Mice were infected with a recombinant vaccinia virus expressing the HIV gp160 envelope gene, and the primed lymphocytes were restimulated *in vitro* with a transfected histocompatible cell line expressing the same gene. H-2^d mice respond predominantly to a single immunodominant site represented by a 15-residue synthetic peptide.

[Takahashi et al.(1989a)] H. Takahashi, R. Houghten, S. D. Putney, D. H. Margulies, B. Moss, R. N. Germain, & J. A. Berzofsky. Structural requirements for class I MHC molecule-mediated antigen presentation and cytotoxic T-cell recognition of an immunodominant determinant of the human immunodeficiency virus envelope protein. *J Exp Med* **170**:2023–2035, 1989a.

NOTE: (Medline: 90063467) Murine BALBc CTL Class I D^d cells elicited by HIV-1 IIIB peptide: RIQRGPGRAFVTIGK.

[Takahashi et al.(1989b)] H. Takahashi, S. Meril, S. D. Putney, R. Houghten, B. Moss, R. N. Germain, & J. A. Berzofsky. A single amino acid interchange yields reciprocal CTL specificities for HIV-1 gp160. *Science* **246**:118–121, 1989b.

NOTE: (Medline: 89388278) Murine BALBc CTL Class I D^d epitope elicited by HIV-1 IIIB and MN gp160 vaccinia construct, stimulated with peptides: RIQRGPGRAFVTIGK, IIIB and RIHIGPGRAYTTKN, MN. These two peptides were non-cross reactive. Val/Tyr exchange was sufficient to interchange the specificities of the two peptides.

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NOTE: (Medline: 92196580) Murine BALBc CTL Class I epitope elicited by HIV-1 RF, IIIB and MN gp160 vaccinia construct, stimulated with peptides: SITKGPGRVIYATGQ, RF; RIQRGPGRAFVTIGK, IIIB; and RIHIGPGRAYTTKN, MN.

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NOTE: (Medline: 92052253) gp41 epitope: RLRDLLLIVTR, HLA A3.1 (NL43). Synthetic peptides of RF and CDC4 were recognized by CTL clone despite non-conservative Thr to (Val or Ala) change, but an MN peptide with four natural substitutions was not recognized.

[Takeshita et al.(1995)] T. Takeshita, H. Takahashi, S. Kozlowski, J. D. Ahlers, C. D. Pendleton, R. L. Moore, Y. Nakagawa, K. Yokomuro, B. S. Fox, D. H. Margulies, & J. A. Berzofsky. Molecular analysis of the same HIV peptide functionally binding to both a class I and a class II MHC molecule. *J Immunol* **154**:1973–1986, 1995.

NOTE: (Medline: 95138543) Of RGPGRAFVTI, the upper case amino acids iGPgRaFvtI are critical for binding, consistent with H-2D^d motif XGPX(RKH)XXX(X)(LIF). Stimulation of the HLA class II I-A^d required a longer peptide, IQRGPGRAFVTI or RIQRGPGRAFVTI, and riqrgPgRaFvtI were essential for binding to the Class II molecule.

[Threlkeld et al.(1997)] S. C. Threlkeld, P. A. Wentworth, S. A. Kalams, B. M. Wilkes, D. J. Ruhl, E. Kepgh, J. Sidney, S. Southwood, B. D. Walker, & A. Sette. Degenerate and promiscuous recognition by CTL of peptides presented by the MHC class I A3-like superfamily. *J Immunol* **159** (4):1648–1657, 1997.

NOTE: (Medline: 97400330) Similarities in peptide binding across A3-like superfamily results in similar peptide-MHC complex structures engaged by T-cell receptors .

[Tobery & Siliciano(1997)] T. W. Tobery & R. F. Siliciano. Targeting of HIV-1 antigens for rapid intracellular degradation enhances cytotoxic T lymphocyte (CTL) recognition and the induction of de novo CTL responses in vivo after immunization. *J Exp Med* **185**:909–20, 1997.

NOTE: (Medline: 97217373).

[Tomiyama et al.(1997)] H. Tomiyama, K. Miwa, H. Shiga, Y. I. Moore, S. Oka, A. Iwamoto, Y. Kaneko, & M. Takiguchi. Evidence of presentation of multiple HIV-1 cytotoxic T lymphocyte epitopes by HLA-B*3501 molecules that are associated with the accelerated progression of AIDS. *J Immunol* **158**:5026–34, 1997.

NOTE: (Medline: 97289618).

[Tsomides et al.(1994)] T. J. Tsomides, A. Aldovini, R. P. Johnson, B. D. Walker, R. A. Young, & H. N. Eisen. Naturally processed viral peptides recognized by cytotoxic T lymphocytes on cells chronically infected by human immunodeficiency virus type 1. *J Exp Med* **180**:1283–1293, 1994.

NOTE: (Medline: 95016420) Naturally processed peptides can be purified from trifluoroacetic acid lysates of HIV-1 infected cells. A gag and RT epitope were compared; both synthetic peptides are optimally active in CTL assays. The naturally processed gag peptide was more abundant than the RT peptide in HIV-1 infected HLA-A2 positive cells, and the gag specific CTL more effective, suggesting surface density of peptides may influence efficiency of CTL killing.

[Tsomides et al.(1991)] T. J. Tsomides, B. D. Walker, & H. N. Eisen. An optimal viral peptide recognized by CD8+ T-cells binds very tightly to the restricting class I major histocompatibility complex protein on intact cells but not to the purified class I protein. *Proc Natl Acad Sci USA* **88**:11276–11280, 1991.

NOTE: (Medline: 92107932).

[van Baalen et al.(1993)] C. A. van Baalen, M. R. Klein, A. M. Geretti, R. I. P. M. Keet, F. Miedema, C. A. C. M. van Els, & A. D. M. E. Osterhaus. Selective *in vitro* expansion of HLA class I-restricted HIV-1 Gag-specific CD8+ T-cells: cytotoxic T-lymphocyte epitopes and precursor frequencies. *AIDS* **7**:781–786, 1993.

NOTE: (Medline: 93371704) Gag specific epitopes and precursor frequencies were studied in seven individuals; for CTLs from one individual, fine mapping was done using peptides. PFA-fixed rVV-Gag-infected B-LCL cells were used as stimulator cells of bulk PBMC cultures to determine precursor frequencies and identify epitopes.

[van Baalen et al.(1996)] C. A. van Baalen, M. R. Klein, R. C. Huisman, M. E. Dings, S. R. Kerkhof Garde, A. M. Geretti, R. Gruters, C. A. van Els, F. Miedema, & A. D. Osterhaus. Fine-specificity of cytotoxic T lymphocytes which recognize conserved epitopes of the gag protein of human immunodeficiency virus type 1. *J Gen Virol* **77**:1659–1665, 1996.

NOTE: (Medline: 96332502).

[van Baalen et al.(1997)] C. A. van Baalen, O. Pontesilli, R. C. Huisman, A. M. Geretti, M. R. Klein, F. de Wolf, F. Miedema, R. A. Gruters, & A. D. M. E. Osterhaus. Human immunodeficiency virus type 1 Rev- and Tat-specific cytotoxic T lymphocyte frequencies inversely correlate with rapid progression to AIDS. *J Gen Virol* **78**:1913–1918, 1997.

NOTE: (Medline: 97410272) CTLp frequencies to Rev and Tat were inversely correlated with rapid progression to AIDS, but not Gag, RT or Nef. 3/7 long term non-progressors and 0/5 progressors were positive for HLA-B57, so it was again found to be associated with long term survival.

[van der Burg et al.(1997)] S. H. van der Burg, M. R. Klein, O. Pontesilli, A. M. Holwerda, J. Drijfhout, W. M. Kast, F. Miedema, & C. J. M. Melief. HIV-1 reverse transcriptase-specific CTL against conserved epitopes do not protect against progression to AIDS. *J Immunol* **159**:3648–3654, 1997.

NOTE: (Medline: 97461484).

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NOTE: (Medline: 95234243).

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HIV CTL Epitopes

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